PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
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Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 June 1999 (25.06.99)	
International application No. PCT/US98/18685	**Applicant's or agent's file reference** MGA-004.25
International filing date (day/month/year) 08 September 1998 (08.09.98)	**Priority date** (day/month/year) 08 September 1997 (08.09.97)
Applicant ELMALEH, David, R. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 April 1999 (08.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Diana Nissen
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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09/530818

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
MGA-004.25		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 18685	08/09/1998	08/09/1997
Applicant		
THE GENERAL HOSPITAL CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

What is claimed is:

1. A cardiovascular imaging agent comprising a radionuclide wherein said radionuclide is associated with a targeting moiety, said targeting moiety comprising an infection-specific agent.

2. The agent of claim 1, wherein said targeting moiety binds to moieties characteristic of an infection process.

3. The agent of claim 2, wherein said infection process is inflammation.

4. The agent of claim 1, wherein said targeting moiety is a leukocyte.

5. The agent of claim 1, wherein said targeting moiety is a protein.

6. The agent of claim 5, wherein said protein is a chemotactic peptide.

7. The agent of claim 6, wherein said chemotactic peptide is For-MLF.

8. The agent of claim 5, wherein said protein is an antibody or fragment thereof.

9. The agent of claim 1, wherein said radionuclide is selected from the group consisting of ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{62}CU , and ^{111}In.

10. The agent of claim 9, wherein said agent comprises the product of combining said targeting moiety or precursor thereof with a chelating compound which chelates said radionuclide.

11. The agent of claim 10, wherein said chelating compound is selected from the group consisting of an $-N_2S_2$ structure, an $-NS^3$ structure, an $-N_4$ structure, an isonitrile, a hydrazine, a HYNIC group-containing structure, 2-methylthiolnicotinic acid group-containing structure, a carboxylate-group containing structure, an amino carboxylate, and a phenolate.

12. The agent of claim 11, wherein said radionuclide is ^{99m}Tc.

13. A method of imaging cardiovascular tissue in a mammal, comprising administering to the mammal said agent of claim 1.

14. The method of claim 13, wherein the method detects a cardiovascular lesion in a mammal, said method comprising the steps of administering to the mammal said agent, detecting the spatial distribution of said agent accumulated in the mammal's cardiovascular system, wherein a detected accumulation of said agent in a region which is different from the detected accumulation of said agent in other regions is indicative of a lesion.

15. The method of claim 14, wherein said cardiovascular lesion is an atherosclerotic lesion.

16. A method of imaging a thrombus in a mammal, comprising administering to the mammal said imaging agent of claim 1.

17. A kit for cardiovascular imaging, comprising a supply of the imaging agent or a precursor of the imaging agent of claim 1.

18. The kit of claim 17, further comprising at least one chelating agent, each chelating agent comprising an auxiliary molecule selected from the group consisting of mannitol, gluconate, glucoheptonate, and tartrate; and a reducing agent.

19. The kit of claim 18, wherein said reducing agent contains tin.

20. The kit of claim 18, wherein the radionuclide of said imaging agent is selected from the group consisting of ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{62}CU , and ^{111}In.

21. The kit of claim 20, wherein said chelating agent(s) is (are) selected from the group consisting of an $-N_2S_2$ structure, an $-NS^3$ structure, an $-N_4$ structure, an isonitrile, a hydrazine, a HYNIC group-containing structure, 2-methylthiolnicotinic acid group-containing structure, a carboxylate-group containing structure, an animo carboxylate, and an amino phenolate.

22. The kit of claim 21, wherein the radionuclide is ^{99m}Tc .

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MGA-004.25		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/18685	08/09/1998	08/09/1997
International Patent Classification (IPC) or national classification and IPC A61K51/08		
Applicant THE GENERAL HOSPITAL CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/04/1999	27.01.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heller, D Telephone No. +49 89 2399 8746

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/18685

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-13 as originally filed

Claims, No.:

1-18 as received on 28/10/1999 with letter of 28/10/1999

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☒ the claims, Nos.: 19-22
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18.

because:

☒ the said international application, or the said claims Nos. 1-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

s separate she t

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	see sections III and V
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section I:

Amendments

The amended claims are allowable under Article 34 (2) b) PCT.

Section III:

Claims 1 to 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V:

Prior art

Reference is made to the following documents:

D1 (HOM R K ET AL: 'Technetium-99m-Labelled Receptor-Specific Small- Molecule Radiopharmaceuticals: Recent Developments and Encouraging Results' NUCLEAR MEDICINE AND BIOLOGY, vol. 24, no. 6, August 1997, page 485-498) describes the use of technetium-99m-labelled receptor-specific small-molecule radiopharmaceuticals (title) for the manufacture of a medicament for routine diagnostic nuclear medicine procedures (page 485, right col., line 10), e.g. perfusion of heart and brain as well as images of renal function (page 485, right col., lines 11 to 20).

D2 (VAIDYANATHAN G ET AL: 'Fluorine-18 Labelled Chemotactic Peptides: A Potential Approach for the PET Imaging of Bacterial Infection' NUCLEAR MEDICINE AND BIOLOGY, vol. 22, no. 6, August 1995, page 759-764) discloses the use of fluorine-18 labelled chemotactic peptides for the PET imaging of bacterial infection (title). The derivatized peptide binds to human polymorphonuclear leukocytes (abstract).

D4 (MAHMOOD A ET AL: 'A New Approach to Labelling Cells with Technetium- 99m, Part I Preparation of Modified Polylysine and In Vitro Cell Labelling' NUCLEAR MEDICINE AND BIOLOGY, vol. 23, no. 1, January 1996, page 79-85) is directed to an approach to label cells with technetium-99m (title). A modified polylysine is labelled with technetium-99m (abstract).

D5 (BABICH J W ET AL: 'Effect of @?Co-ligand@? on the Biodistribution of Tc-labelled Hydrazine Nicotinic Acid Derivatized Chemotactic Peptides' NUCLEAR MEDICINE AND BIOLOGY, vol. 22, no. 1, January 1995, page 25-30) relates to the effect of "co-ligand"on the biodistribution of ^{99m}Tc-labelled hydrazine nicotinic acid derivatized chemotactic peptides (title). Said compounds are useful for infection imaging (abstract).
D5 is authored by the inventors of the present application.

D8 (EP-A-0 419 203) provides a method for direct radiolabelling of a monovalent, e.g.,. Fab or Fab', antibody fragment which is rapid and convenient and which results in a labelled fragment ready for direct injection into a patient (col. 1, lines 40 to 45).

D9 (WO 95 06633 A) is related to chelators that bind diagnostically and therapeutically useful metal radionuclides, and can be conjugated to targeting agents such as proteins and peptides (page 9. lines 3 to 5) capable of localizing at body sites of diagnostic and therapeutic interest, e.g. atherosclerotic plaque (page 9, lines 3 to 5). The chelators of the present invention are peptide analogues designed structurally to present an N_2S_2 configuration capable of binding oxo, dioxo and nitrido ions of ^{99m}technetium and $^{186/188}$rhenium (page 2, lines 16 to 21).

D10 (WO 95 03280 A) is directed to the same subject as D9. The chelators of the present invention are peptide analogues designed structurally to present an N_3S configuration capable of binding oxo, dioxo and nitrido ions of ^{99m}technetium and $^{186/188}$rhenium (page 2, lines 31 to 37).

D12 (WO 95 11045 A) relates to a substantially non-invasive method for imaging infection or inflammation sites based upon the discovery that detectably labelled chemotactic peptides injected systemically into animals accumulate at sites of local infection (page 8, lines 25 to 28).

D13 (WO 93 12819 A) relates to protein-based and peptide-based metal ion-labelled compositions for use as pharmaceuticals, and methods of labelling peptides, proteins and other similar substances with radiometals, paramagnetic metals and other medically useful metal ions, and further providing for use of medically useful metal ionlabelled peptides for detection of thrombus, cancer, infection, inflammation and various lung diseases, pathologies and abnormalities (page 1, lines 5 to 13).

D14 (WO 91 02547 A) is concerned with scintigraphic detection of thrombi in mammals including humans. However, substances and processes developed to facilitate detection of thrombi may also have usefulness for other imaging such as of tumours. It has already been proposed to label various proteins for antibodies with radiometal ions for scintigraphic or therapeutic applications. Labelling has been with technetium-99m because of its advantageous physical properties. Of particular interest has been the use of monoclonal antibodies raised against specific antigens (page 1, lines 9 to 19).

D15 (WO 90 10463 A) involves improved imaging of tissue sites of inflammation. Improved diagnostic images result from an increase in the number of labelled leukocytes in the area of the inflammation or from improved selectivity of antibodies or peptides for activated leukocytes in sites of inflammation versus non-activated leukocytes in the circulation (page 1, lines 5 to 12).

D16 (WO 97 10853 A) is directed to the use of chelators containing nicotinamide as a medicament for the radio diagnosis (page 1, lines 4 to 11). Metallic radionuclides, especially technetium-99m are use for said diagnosis (page 2, lines 10 to 12).

D6 (LIU S ET AL: 'Tc-labelling Kinetics of Four Thiol-containing Chelators and 2-Hydrazinopyridine: Factors Influencing Their Radiolabelling Efficiency' APPLIED RADIATION AND ISOTOPES, vol. 48, no. 8, August 1997, page 1103-1111) describes the ^{99m}Tc-labelling kinetics of four thiol-containing chelators and 2- hydrazinopyridine.

D11 (WO 96 31243 A) relates to novel radiopharmaceuticals which are useful as imaging agents for the diagnosis of cardiovascular disorders, infectious disease and cancer, and to kits useful for their preparation. The radiopharmaceuticals are

comprised of phosphine or arsine ligated technetium-99m labelled hydrazine or diazino modified biologically active molecules that selectively localize at sites of disease and thus allow an image to be obtained of the loci using gamma scintigraphy (page 1, lines 15 to 24; page 5, lines 14 to 28).

Novelty

The subject-matter of claims 1 to 18 is not new in the sense of Article 33 (2) PCT.

Generally, every imaging agent comprising the same as in claim 1 which is suitable to be administered cardiovascular, anticipates novelty of present claim 1.
Therefore, for the present claims 1 to 18 the following applies:

D1 anticipates novelty of claims 1, 2 (page 485, left col., §1), 3, 6 and 7 (page 492, right col., molecule no. 29), 8 to 11 (page 485, right col., lines 18 to 20).

D2 anticipates novelty of present claims 1, 2, 5 (abstract), 8 to 12 (table 1).

D4 anticipates novelty of present claims 1, 2 5.

D5 anticipates novelty of present claims 1 to 4, 6 and 7, 8 to 11 (table 1), 12 to 18 (table 1; page 27, right col., §3).

D8 anticipates novelty of claims 1 to 4, 6 and 7, 8 to 11, 12, 13 (col. 2, lines 12 to 20), 14 to 17.

D9 anticipates novelty of claims 1 to 4, 6 and 7 (example 4), 8 to 11, 12 to 17.

D10 anticipates novelty of claims 1 to 4, 6 and 7, 8 to 11, 12 to 14 (example 12), 15 to 17.

D12 anticipates novelty of present claims 1, 2 (page 27, lines 1 to 15), 3, 4, 5 (page 75, example 102), 6 and 7 (page 26, lines 1 to 8), 8 to 11 (page 52, lines 20 to 27), 12 to 18 (example 102).

D13 anticipates novelty of present claims 1, 2 (example 2), 3, 4, 6 and 7 (page 1, last line), 8 to 11, 12 to 17 (example 2).

D14 anticipates novelty of present claims 1, 2, 4 (claim 8), 8 to 11, 12 to 14 (example 2, item 4.), 15.

D15 anticipates novelty of present claims 1 to 3 (claims 1 and 7), 4, 5, 6 and 7 (claim 30), 8, 9, 10 and 11, 12, 13 to 17, 18, 19 (example 10), 20 to 22.
1, 2 (claim 7), 3, 4 (example 1), 5, 6 and 7 (claim 2), 8 to 11 (claim 4), 12 to 14 (example 10), 15 to 18.

D16 anticipates novelty of present claims 1 to 3 (page 4, line 16), 6 and 7 (page 6, lines 26ff), 8 to 11 (claim 15), 12 to 14 (page 4, lines 31 to 35), 15 to 17.

As D6 is silent to the targeting moiety, it does not anticipate novelty of present claims.

As D11 contains another compound (with phosphine or arsine), it does not anticipate novelty of present claims.

Inventive step

Even if the applicant is able to establish novelty it cannot be seen that any particular aspect of the application as filed would involve an inventive step under Article 33 (3) PCT in the light of the relevant prior art.

Industrial applicability

For the assessment of the present claims 1 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI:

The applicant should pay attention to D3 and D7 (D3: WELLING M ET AL: 'Detection of Experimental Infections with Tc-Labelled Monoclonal Antibodies Against TNF-alpha and Interleukin-8' NUCLEAR MEDICINE AND BIOLOGY, vol. 24, no. 7, October 1997, page 649-655; D7: DINKELBORG L. M. ET AL: 'Molecular imaging of atherosclerosis using a technetium-99m-labelled endothelin derivative' J. NUCL MED, vol. 39, no. 10, October 1998, pages 1819-1822, XP002089860 & DINKELBORG L. M. ET AL: 'Characterization of a technetium-99m-endothelin derivative for imaging atherosclerosis in a rabbit balloon denudation model' J NUCL MED, vol. 38, no. suppl, 1997, page 173p) which does not constitute prior art within the meaning of Rule 64.1 (b) PCT and which could be relevant as a state in the art document in the national phases, if the priority is not valid.

Section VIII:

Article 6 PCT

The terms "component of a process involved in plaque formation", "auxiliary molecule and "... cells, ..." used in claims 1/12, 4 and 5/18 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

The features of claims 7 and 16 "amino carboxylate, phenolate and amino phenolate" are not referred to in the description. Claims 7 and 16 are therefore not supported by the description as required by Article 6 PCT.

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